In the Claims

Please cancel claims 7, 21-31, 34, 36-39, 41, 45-62, 69-71, 73-78 and 82-87, without prejudice. Please amend claims 8-12, 32, 35, 40, 42, 63, 65, 79, 88, and add claims 101-109 as presented below in amended form:

In claims 8-12 and 93, please replace "7" with "101"

In claim 32, please raptace "31" with "104".

In claim 42, please replace "26" with "41".

In claim 63, please replace "62" with "107".

In claim 79, please replace "78" with "108".

In claim 88, please replace "82" with "109".

35. (Amended) The method of claim 104 wherein R_1 is dimethoxytrityl, A has the formula -O-(CH_2)_n-NH- where n is 6, m is 2, R_4 is t-butoxy, R_5 is trifluoroacetoyl, R_6 is -C(=O)- $CH(CH_3)_2$, and R_{30} is FMOX.



40. (Amended) The method of claim 105 wherein R_1 is dimethoxytrityl, W_1 has the formula -O-(CH₂)_n-NH- where n is 6, m is 2, R_4 is t-butoxy, R_5 is trifluoroacetoyl, R_6 is -C(=O)-CH(CH₃)₂, and R_{30} is FMOX.

65. (Amended)

The compound of claim 64 wherein R_4 is t-butoxy.

101. (New) A compound having formula XVIA, XVIB, XVIC or XVID:

£7

wherein:

W₁₄ has the formula

PATENT

$$-x_{6}-x_{5}-x_{4}-\underset{H}{\overset{O}{\bigvee}}$$

wherein:



 X_4 is -CH(X_4) or a group of formula:

 $X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

 $X_5 \, is \, \text{-N}(X_6) C(O) \text{--, -C}(O) NH \text{--, -NHC}(O) \text{--, -OC}(O) NH \text{--, -C}(S) NH \text{--, -SC}(S) NH \text{--, -SC}(O) NH \text{--, -SC}(O) NH \text{--, -C}(O) CH_2)_n \text{--} or a bond;$

PATENT

n is an integer from 1 to 50;

each X_6 and X_6 is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, C_5 - C_{14} fused cycloalkyl, C_4 - C_{14} heterocycle, C_4 - C_{14} heterocyclylalkyl, C_4 - C_{14} heteroaryl and C_4 - C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6 is not a bond;

R₁ is hydrogen or a hydroxyl protecting group;

R₄ is a hydroxyl group or a protected hydroxyl group;

each R_5 and R_{40} is, independently, hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl or an amino-protecting group

 $R_{5''} \ is \ hydrogen, C_1-C_{10} \ alkyl, C_2-C_{10} \ alkenyl, C_2-C_{20} \ alkynyl, C_6-C_{14} \ aryl, C_6-C_{14} \ aralkyl, C_3-C_{14} \ cycloalkyl, formyl, aminoalkyl or hydroxymethyl;$

R₆ is hydrogen or an amino protecting group;

R₂₀ is hydrogen or a group of formula:

$$R_3-O$$
 P
 R_2

 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms,

PATENT

and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

R₂₁ is hydrogen, hydroxyl, fluoro or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH or N- R_{22} - $(R_{23})_v$;

 R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R₂₁ has one of the formulas:



$$---(O)_{y_1} - ---(CH_2)_{y_2} - O - N - ----(CH_2)_{y_2} - O - E$$

wherein:

v1 is 0 or 1;

PATENT

each y2 is, independently, 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

q is 0 to about 50; and

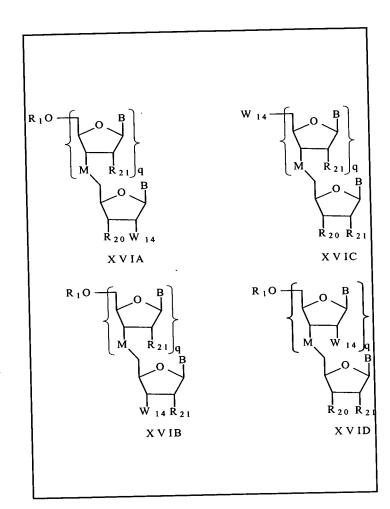
v is from zero to about 10;

provided that when said compound has formula XVID, q is at least 1.



PATENT

102. (New) A compound having formula XVIA, XVIB, XVIC or XVID:





wherein:

W₁₄ has the formula:

$$-X_{6}-X_{5}-X_{4}-N$$
 X_{9}
 X_{9}
 X_{1}
 X_{1}
 X_{1}
 X_{1}
 X_{2}
 X_{3}
 X_{4}
 X_{5}
 X_{5}
 X_{7}
 X_{1}
 X_{1}
 X_{1}
 X_{2}
 X_{3}
 X_{4}
 X_{5}
 X_{5}



wherein:

 X_4 is -CH(X_4) or a group of formula:

$$-(CH_2)_t$$

 X_4 is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

 $X_5 \text{ is -N}(X_6)C(O)\text{--, -C}(O)NH\text{--, -NHC}(O)\text{--, -OC}(O)NH\text{--, -C}(S)NH\text{--, -SC}(S)NH\text{--, -SC}(O)NH\text{--, -C}(O)O\text{--, -C}(O)(CH_2)_n\text{-- or a bond;}$

n is an integer from 1 to 50;

each X_6 , X_6 and X_9 is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, C_5 - C_{14} fused cycloalkyl, C_4 - C_{14} heterocycle, C_4 - C_{14} heterocyclylalkyl, C_4 - C_{14} heteroaryl and C_4 - C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that each X_6 and X_9 is not hydrogen and X_6 is not a bond;

R₁ is hydrogen or a hydroxyl protecting group;

R₄ is a hydroxyl group or a protected hydroxyl group;

each $R_{5'}$ and R_{40} is, independently, hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl or an amino-protecting group

 $R_{5"} is \ hydrogen, C_1-C_{10} \ alkyl, C_2-C_{10} \ alkenyl, C_2-C_{20} \ alkynyl, C_6-C_{14} \ aryl, C_6-C_{14} \ aralkyl, C_3-C_{14} \ cycloalkyl, formyl, aminoalkyl or hydroxymethyl;$

R₆ is hydrogen or an amino protecting group;

 R_{20} is hydrogen or a group of formula:

$$R_3-O$$
 P
 R_2

 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

R₂₁ is hydrogen, hydroxyl, fluoro or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH or N- R_{22} - $(R_{23})_v$;

 R_{22} is $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, or $C_2\text{-}C_{20}$ alkynyl;



PATENT

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:

$$(CH_2)_{y_2}$$
 $O - E$

wherein:

y1 is 0 or 1; each y2 is, independently, 0 to 10; y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom

PATENT

selected from N and O;

B is a nucleobase;

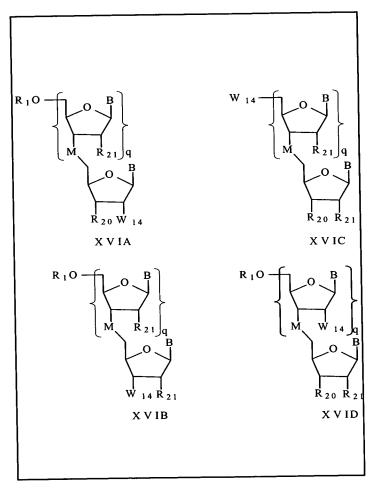
M is an optionally protected internucleoside linkage;

q is 0 to about 50; and

v is from zero to about 10;

provided that when said compound has formula XVIC, at least one R_{21} is a group other than hydrogen, and when said compound has formula XVIC or XVID, q is at least 1.

103. (New) A compound having formula XVIA, XVIB, XVIC or XVID:





XVIB

XVID

wherein:

W₁₄ has the formula:

$$-x_6-x_5-x_4-N \longrightarrow R_5" \longrightarrow CH_3 \longrightarrow O \longrightarrow NH \longrightarrow R_6$$

(V)

wherein:

 X_4 is -CH(X_4) or a group of formula:

PATENT

 $X_{4'}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

 $X_5 \text{ is -N}(X_6)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -C(S)NH-, -SC(S)NH-, -SC(O)NH-, -OC(S)NH-, -C(O)O-, -C(O)(CH_2)_n- or a bond;$

n is an integer from 1 to 50;

each X_6 and X_6 is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl, C_6 - C_{14} aralkyl, C_3 - C_{14} cycloalkyl, C_5 - C_{14} fused cycloalkyl, C_4 - C_{14} heterocycle, C_4 - C_{14} heterocyclylalkyl, C_4 - C_{14} heteroaryl and C_4 - C_{14} heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6 is not a bond;

R₁ is hydrogen or a hydroxyl protecting group;

R₄ is a hydroxyl group or a protected hydroxyl group;

each $R_{5'}$ and R_{40} is, independently, hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{20} alkynyl, C_6 - C_{14} aryl or an amino-protecting group

 $R_{5"} is \ hydrogen, C_{1}-C_{10} \ alkyl, C_{2}-C_{10} \ alkenyl, C_{2}-C_{20} \ alkynyl, C_{6}-C_{14} \ aryl, C_{6}-C_{14} \ aralkyl, C_{3}-C_{14} \ cycloalkyl, formyl, aminoalkyl or hydroxymethyl;$

R₆ is hydrogen or an amino protecting group;

R₂₀ is hydrogen or a group of formula:

$$R_3-O$$
 P
 R_2

 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;



PATENT

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

 R_{21} is hydrogen, hydroxyl, fluoro or a group of formula Z- R_{22} -(R_{23}),;

Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

 R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R₂₁ has one of the formulas:

$$(CH_2)_{y2}$$
 $O - E$

$$---(O)_{y1} - ---(CH_2)_{y2} - O - N - ----(CH_2)_{y2} - O - E$$

PATENT

wherein:

y1 is 0 or 1; each y2 is, independently, 0 to 10; y3 is 1 to 10; E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

q is 0 to about 50; and

v is from zero to about 10;

provided that when said compound has formula XVID, q is at least 1.



PATENT

104. (New) A synthetic method comprising the steps of:

(a) providing a compound of formula IA, IB, IC or ID:

ΙA

$$R_1$$
—O B
 W_1a
 q
 R_{20}
 R_{21}
ID

PATENT

wherein:

W_{1a} is W_{1b}-H, OH, NH₂ or SH, where W_{1b} is a linking group;

R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

Z is O, S, NH, or N- R_{22} - $(R_{23})_v$

 R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R₂₁ has one of the formulas:

$$(O)_{y_1}$$
 $-(CH_2)_{y_2}$ $O - E$

$$--(O)_{y1} - (CH_2)_{y2} - O - N - (CH_2)_{y2} - O - E$$

wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from zero to about 50, provided that when said compound has formula ID, q is at least 1;

M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

II

wherein:

 R_{30} is an amino protecting group;

 X_3 is a group of formula XII:

$$\{$$
 $\}_{m}$

XII

wherein m is 1 or 2;

PATENT

 R_4 is a hydroxyl group, or a protected hydroxyl group; to form a compound of formula IVA, IVB, IVC, or IVD:

$$W_{4} = \begin{bmatrix} O & B \\ & &$$

wherein:

W₄ has the formula:

IVC

where W_1 is a linking group, O, NH, or S; and treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a

compound of formula VA, VB, VC or VD:

$$R_1$$
-O O B R_{21} Q O B W_5 R_{21} VB

$$W = \begin{bmatrix} O & B \\ R_{21} & q \\ Q & R_{21} \end{bmatrix}$$

$$V = \begin{bmatrix} O & B \\ R_{20} & R_{21} \\ V & C \end{bmatrix}$$

$$R_1$$
— O
 M
 W_5
 Q
 R_{20}
 R_{21}
 VD

wherein W₅ has the formula:

(c) condensing said compound of Formula V with a compound of Formula VI:

PATENT

VI

wherein:

 R_5 is H or an amino protecting group;

R₆ is H or an amino protecting group;



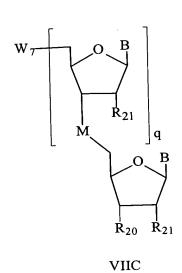
PATENT

to form a compound of Formula VIIA, VIIB, VIIC, or VIID:

VIIA

VIIB





$$R_1$$
— O
 M
 W_7
 q
 R_{20}
 R_{21}

VIID

wherein W₇ has the Formula:

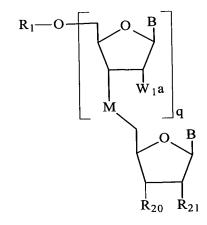
$$\{-W_1-C-X_3-NH \bigcup_{O} \bigvee_{R_5} \bigvee_{N} \bigvee_{N} \bigvee_{N} \bigvee_{N} \bigvee_{N} H$$

PATENT

105. (New) A synthetic method comprising the steps of:

(a) providing a compound of formula IA, IB, IC or ID:

$$R_1$$
-O B
 R_{21}
 q
 W_1a
 R_{21}



ID

PATENT

wherein:

 W_{1a} is W_{1b} -H, OH, NH₂ or SH, where W_{1b} is a linking group;

R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH, or N- R_{22} - $(R_{23})_v$

 R_{22} is $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, or $C_2\text{-}C_{20}$ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R₂₁ has one of the formulas:

$$--(O)_{y_1} - (CH_2)_{y_2} - O - N - (CH_2)_{y_2} - O - E$$

PATENT

wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from zero to about 50, provided that when said compound has formula ID, q is at least 1;

M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

$$R_{30}$$
—NH $-X_3$ -C-OH

Π

wherein:

 R_{30} is an amino protecting group;

 X_3 is a group of formula XII:

$$\{$$
 $\}_{m}$

XII

wherein m is 1 or 2;

PATENT

 R_4 is a hydroxyl group, or a protected hydroxyl group; to form a compound of formula IVA, IVB, IVC, or IVD:

$$R_1$$
-O O B R_{21} q O B R_{20} W_4 IVA

$$\begin{array}{c|c} W & \bullet & \bullet & \bullet \\ \hline & M & & Q & \bullet \\ \hline & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & \\ & & \\ & \\ & & \\ & & \\ & \\ & & \\ & & \\$$

$$R_1$$
— O
 W_4
 Q
 R_{20}
 R_{21}
IVD

wherein:

 W_4 has the formula:

IVC

where W_1 is a linking group, O, NH, or S; and treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a

PATENT

compound of formula VA, VB, VC or VD:

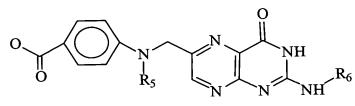
$$R_1$$
— O
 M
 W_5
 Q
 R_{20}
 R_{21}
 VD

wherein W₅ has the formula:

$$\left\{ \begin{matrix} O \\ \parallel \\ - V_1 \end{matrix} \begin{matrix} O \\ \parallel \\ C - X_3 - NH_2 \end{matrix} \right\}$$
 and

PATENT

(c) condensing said compound of Formula V with a compound of Formula VI:



VI

wherein:

R₅ is H or an amino protecting group;

R₆ is H or an amino protecting group;



PATENT

to form a compound of Formula VIIA, VIIB, VIIC, or VIID:

VIIB



$$W_{7} = \begin{bmatrix} O & B \\ & &$$

VIIC

$$R_1$$
— O B W_7 q O B R_{20} R_{21}

VIID

PATENT

wherein W₇ has the Formula:

(d) contacting said compound of Formula VIIA or VIID with a phosphitylating reagent to form a compound of Formula VIIIA or VIIID:



wherein W₇ has the Formula:

PATENT

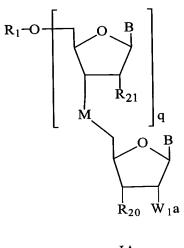
$$\{-w_1-C-x_3-NH \bigcup_{O} \bigvee_{R_5} \bigvee_{N} \bigvee_{N} \bigvee_{NH} \bigcap_{R_6}$$

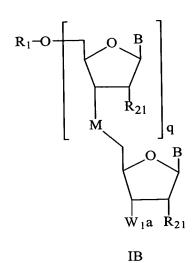


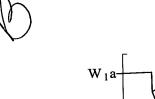
PATENT

A synthetic method comprising the steps of: 106 (New).

providing a compound of formula IA, IB, IC or ID: (a)







$$W_1a$$
 Q
 B
 R_{21}
 Q
 R_{20}
 R_{20}

$$R_1$$
—O B
 W_1a
 q
 R_{20} R_{21}

ID

PATENT

wherein:

W_{1a} is W_{1b}-H, OH, NH₂ or SH, where W_{1b} is a linking group;

R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH, or N- R_{22} - $(R_{23})_v$

 R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R₂₁ has one of the formulas:

$$(CH_2)_{y2}$$
 $O - E$



wherein:

y1 is 0 or 1;

y2 is 0 to 10;

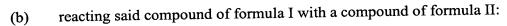
y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from zero to about 50, provided that when said compound has formula ID, q is at least 1;

M is an optionally protected internucleoside linkage;



$$R_{30}$$
—NH $-X_3$ -C-OH

 Π

wherein:

R₃₀ is an amino protecting group;

 X_3 is a group of formula XI:

$$\left\{ \begin{array}{c} --(CH_2)_p \\ R \end{array} \right\}$$

ΧI

wherein:

p is 1 or 2;

PATENT

 R_4 is a hydroxyl group, or a protected hydroxy group; or X_3 is a group of formula XII:

XII

wherein m is 1 or 2;

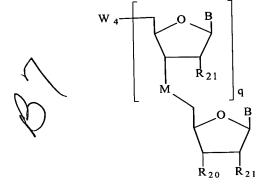
 Z_1 is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

 R_4 is a hydroxyl group, or a protected hydroxyl group; p is 1 or 2; to form a compound of formula IVA, IVB, IVC, or IVD:



PATENT

$$R_1$$
-O \xrightarrow{O} \xrightarrow{B} \xrightarrow{Q} \xrightarrow{W} \xrightarrow{A} \xrightarrow{R} \xrightarrow{Q} \xrightarrow{IV} \xrightarrow{B}



wherein:

W₄ has the formula:

IVC

where W_1 is a linking group, O, NH, or S; and treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a compound of formula VA, VB, VC or VD:

PATENT

$$R_1$$
-O B
 R_{21}
 q
 R_{20}
 W
 S
 S

$$R_1 \longrightarrow O \longrightarrow O \longrightarrow B$$
 $M \longrightarrow Q$
 $R_{20} \longrightarrow R_{21}$
 VD

wherein W₅ has the formula:

(c) condensing said compound of Formula V with a compound of Formula VI:

PATENT

$$O \longrightarrow N \longrightarrow NH$$

$$R_5 \longrightarrow N \longrightarrow NH$$

$$R_6$$

VI

wherein:

 R_5 is H or an amino protecting group;

R₆ is H or an amino protecting group;

to form a compound of Formula VIIA, VIIB, VIIC, or VIID:



PATENT

$$R_1$$
-O O B R_{21} q W_7 R_{21} VIIB

VIIA

$$\mathcal{O}$$

$$W_{7} = \begin{bmatrix} O & B \\ & &$$

VIIC

$$R_1$$
—O B
 W_7
 q
 R_{20} R_{21}

VIID

wherein W₇ has the Formula:

wherein said compound of formula VI is prepared by the steps of reacting a compound of formula IX:

8

with a compound of formula X:

$$H_2N$$
 C
 C
 C
 C
 C

and treating the product of said reaction with a protecting group reagent to form said compound of formula VI.

PATENT

107. (New) A compound having the formula XIIIA, XIIIB, XIIIC or XIIID:

$$\begin{array}{c} R_1 - O \\ \hline \\ M \end{array} \begin{array}{c} O \\ R_{21} \end{array} \begin{array}{c} B \\ Q \\ R_{20} \end{array} \begin{array}{c} W \\ 13 \end{array}$$



$$W_{13} = \begin{bmatrix} O & B \\ R_{21} \end{bmatrix}_{q}$$

$$R_{20} = R_{21}$$

XIIID

wherein:

W₁₃ has the formula:

R₁ is H or a hydroxyl protecting group;

PATENT

B is a nucleobase;

each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

 R_{22} is C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, or C_2 - C_{20} alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:

PATENT

wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

v is from 0 to about 10;

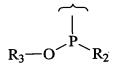
q is 0 to about 50; and

v is from zero to about 10;

M is an optionally protected internucleoside linkage;

W₁ is a linking group, O, NH or S;

R₂₀ is H or a group of Formula:



 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

R₅ is H or an amino protecting group;

R₆ is H or an amino protecting group;

X₃ has the formula XII:



PATENT

XII

wherein m is 1 or 2;and

 R_4 is a hydroxyl group, or a protected hydroxyl group; provided that when said compound has formula XIIIC, at least one R_{21} is a group other than hydrogen, and when said compound has formula XIIIC or XIIID, q is at least 1.



PATENT

108 (New) A compound having the formula XVIA, XVIB, XVIC or XVID:

$$R_1$$
-O B
 R_{21}
 Q
 R_{20}
 W_{16}

XVIA



XVIC

$$R_1$$
—O B
 W_{16}
 q
 R_{20}
 R_{21}

XVID

PATENT

wherein:

W₁₆ has the formula:

R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

Z is O, S, NH or N- R_{22} - $(R_{23})_v$;

 $R_{22}\,is\,C_1\text{-}C_{20}\,alkyl,\,C_2\text{-}C_{20}\,alkenyl,\,C_2\text{-}C_{20}\,alkynyl,\,C_1\text{-}C_{20}\,akoxy,\,C_2\text{-}C_{20}\,alkenyloxy,\\$ or $C_2\text{-}C_{20}\,alkynyloxy;$

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R₂₁ has one of the formulas:

$$-[(O)_{y1}-(CH_2)_{y2}]_{y3}O-E$$

wherein:

PATENT

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

v is from 0 to about 10;

q is 0 to about 50;

M is an optionally protected internucleoside linkage;

W₁ is a linking group;

R₂₀ is H or a group of Formula:



$$R_3$$
—O $\stackrel{\frown}{P}$ R_2

 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

X₃ has the formula XII:

$$\{$$
 $\}_{m}$

XII

PATENT

wherein m is 1 or 2;

 R_4 is a hydroxyl group, or a protected hydroxyl group; and provided that when said compound has formula XVID, q is at least 1.



PATENT

109. (New) A compound having the formula XVIIA, XVIIB, XVIIC or XVIID:

XVIIA

XVIIB





$$R_{20}$$
 R_{21} XVIIC

$$\begin{bmatrix} M & W_{17} \\ Q & R_{20} \end{bmatrix} \stackrel{Q}{\underset{R_{20}}{}}$$

XVIID

wherein:

 W_{17} has the formula:

$$\{-w_1 - C - x_3 - NH \}$$

R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH or N- R_{22} - $(R_{23})_v$;

 R_{22} is $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, or $C_2\text{-}C_{20}$ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R_{21} has one of the formulas:

$$-[(O)_{y1}-(CH_2)_{y2}]_{y3}O-E$$

$$----(O)_{y_1} - - (CH_2)_{y_2} - O - N - - (CH_2)_{y_2} - O - E$$

wherein:

y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

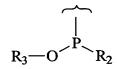
v is from 0 to about 10;

q is 0 to about 50;

M is an optionally protected internucleoside linkage;

W₁ is a linking group, O, NH or S;

R₂₀ is H or a group of Formula:



 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

 X_3 has the formula XII:

XII